International Journal of Chemical &
Petrochemical Technology (IJCPT)
ISSN(P): 2277-4807; ISSN(E): 2319-4464
Vol. 3, Issue 5, Dec 2013, 1-8

STUDY OF ATENOLOL AND METOPROLOL SORPTION BEHAVIOR ON NATURAL SEDIMENT

ZAHRA FONA

Department of Chemical Engineering, State Polytechnic of Lhokseumawe, Indonesia

ABSTRACT

The characteristics of two cationic organic pharmaceutical compounds, Metoprolol and Atenolol have been simulated in laboratory experiments. The objective of the present research was to characterize the sorption of the two similar compounds onto natural sediment and to correlate the competition effect of the compounds with inorganic cations by means of column experiments.

Tap water with additional of certain inorganic cations from salt solutions (Ca^{2+}, Mg^{2+}, K^{+}, and Na^{+}) was used as model water in the experiment in order to mimic natural condition. Flow of water into column was kept 0.5 ml/min. Both compounds were tested in the separate process of column experiment under a similar boundary condition (T = 10 ^{o}C). Sample was taken every ten minute from the column outlet using fraction collector. The compound concentrations were analyzed using HPLC under isocratic mobile phase of 0.3 ml/min flowrate. The retardation factors of both compounds were determined. The study showed the retardation factor of 10 was obtained for metoprolol instead of 4.7 for Atenolol. Metoprolol showed a strong tailing in the breakthrough curve. The result indicated that Metoprolol has a stronger sorption than Atenolol.

KEYWORDS: Cationic Organic Compound, Pollutant Behavior, Sorption, Pharmaceutical, Retardation, Atenolol, Metoprolol, Sediment

INTRODUCTION

The input of pharmaceuticals into river becomes an interesting topic in various fields of study. Although they have been found relatively low concentration in aquatic environment, the continuous contribution indirectly from Sewage Treatment Plants (STPs) and directly as well can be definitely problematic in future. Additionally, there is an indication of increasing pharmaceuticals consumption all over the world due to the increasing of population. Because of the incomplete elimination by STPs (Valcarcel et al., 2011), the compounds existence in the environment continues to grow.

As a result, many types of pharmaceuticals and their transformation products seemed to remain in the water (Farre et al., 2008). On one hand, biodegradation and adsorption process could be occurred. On the other hand, it is obvious that almost all types of pharmaceuticals consisting more than 80 compounds (Heberer, 2002) as well as their metabolites, found in the effluent of STPs. This may create problem to rivers and streams (Lundström et al., 2010; Vieno, et al., 2006), and can reach groundwater (Farre et al., 2008).

The concentrations of the micro organic pollutants have been found in trace level in aquatic environment (Gros, 2006). However, the constant input into aquifer can induce the concentrations of some particular compounds to increase. Although the long term effect on aquatic lives as well as human health is still unknown, potential harmful might be developed. In addition, cumulative effect could be involved and increased by using recycling water. For instance, the consumption of groundwater from infiltration, and the use of river water from effluent of STPs (Bendz et al., 2005).

Atenolol and Metoprolol are pharmaceutical compounds categorized in the group of beta blocker (β-blocker) – beta adrenoreceptor blocking. They are odorless powders which are relatively polar and therefore hydrophilic. The substances are used in the treatment of hypertension and angina pectoris. The principle effect of beta-adrenoreceptor blockers is to reduce cardiac activity by reducing the rate and force of contraction.

Molecular formulas of Atenolol and Metoprolol are respectively $C_{14}H_{22}N_2O_3$ and $C_{15}H_{25}NO_3$. The structural formulas are shown in Figure 1.

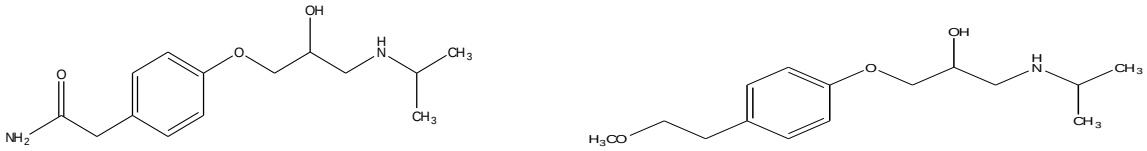

Figure 1: Structure of (a) Atenolol (b) Metoprolol

The consumption of Atenolol and Metoprolol has been long time in many countries over the world, particularly European countries and North America (Song et al, 2008). They are among the most consuming drugs in the world beside Propanolol (Sires, 2010). The compounds existence in river water in Germany has been found in nanogram/liter (Table 1).

Table 1: The Occurrence of Atenolol and Metoprolol in River in Germany

Name of Compound, Formula Investigated Rivers	Pk_a	Consumption	Concentration In River, Mean/Max (Ng/L)
Atenolol, $C_{14}H_{22}N_2O_3$ 15 rivers (2000-2001) 4 rivers: Koersch, Schwarzbach, Oker, Elbe, (2000-2001) River Rhine (2010)	9.40[b]; 9,16[e];9.60[f]	5.2-10.5 t/a[a]	< LOQ/70[c] 27/90[c] 15/27[i]
Metoprolol, C15H25NO3 15 rivers (2000-2001) 4 rivers: Koersch, Schwarzbach, Oker, Elbe (2000-2001)River Rhine (2010)	9.70; 9.60[d]	55.5-111 t/a[a]	17/1800[c] 117/260[c] 42/200[g]

[a]Cleuvers(2005), [b]Martinez,(2000), [c]BLAC(2003),
[d]http://www.syrres.com/what-we-do/databaseforms.aspx?id=386,
[e]Yamamoto et al., 2009, [f] Gros et al. (2006), [g]Ter Laak (2010)

Deeper attention to the compounds is indispensable. They often have specific characteristics in the environment such as strong interaction to the soil. Although Atenolol can be degraded by biological activities but the underground conditions are not infinitely encouraged. Nevertheless, it still lacks of information regarding the particular polar organic pollutants behavior in environment and thus remains a big challenge for further investigations.

This work was focused on the polar organic micro pollutant behavior, Atenolol dan Metoprolol which are not included in the legislation but has likely detrimental effects on aquifer; not only drinking water resources but also general aquatic environment. They can be appeared as cationic forms in the water. Anionic forms are generally unsophisticated to go after polar solvent. By contrast, cationic forms have specific characteristics i.e. water soluble and persistent to environment. Hence, cationic micro pollutants attract more attention of scientific fields due to their elaborate behavior.

To deal with its existence in the environment and at the end to prevent further aquifer contamination, the substantial characteristics should be investigated. Field monitoring and investigating can be costly and time consuming. In addition, it is complicated and devious. Therefore, a small scale method has been developed as an appropriate simulation. Laboratory column experiments were carried out using natural sandy sediment from Greek to mimic and simplify natural condition. Finally, the observation would be very valuable and generous for further virtual application in identifying the fate of trace polar cationic organic compounds in aquifer.

Study on the behavior of Atenolol and Metoprolol was conducted in Institute of Water Chemistry, University of Technology Dresden. Schaffer (2012), studied that Atenolol was significantly influenced by the main boundary condition and natural sediment properties. Atenolol was found to have strong retardation in spite of it high polarity. In this research, the sorption behavior of another compound, Metoprolol which has similar characteristic with Atenolol was investigated as well. The sorption characteristics of both compounds were compared in order to find out the effect of the nature of compound to the sorption. In addition, it was subjected to acquire information on such competition influence of inorganic cations on the sorption.

MATERIALS AND METHODS

Materials

Greek sediment was used in column experiment as sorbent material without purification. The pharmaceuticals studied in this work were Atenolol which was purchased from Fagron with a purity of 99.3% and Metoprolol in the form of Metopolol tartrate 99% from Sigma- Aldrich. NaCl, $CaCl_2$, , KNO_3, were from Th. Geyer, VWR, and Riedel-de Haën, respectively. KCl, $MgCl_2$, Na_2SO_4, $NaHCO_3$ were from Merck. Daily household consumption of tap water from Coschütz Waterworks Dresden was utilized for all model water. Model water was the tap water after additional some salts (as shown in Table 2).

HPLC grade acetonitrile and ammonium hydrogen carbonate were applied for analytical measurements of the pharmaceutical compounds. They were obtained from Baker and Merck, respectively. The HPLC grade water was used for any analytical solution for HPLC.

METHODS

Column Filling

Column for the experiment made of stainless steel diameter of 3.42 cm and height of 25 cm was filled with Greek sediment. Approximately 500 grams of sediment was mixed with 40 ml tap water and filled into the column. It was pressed with a tamper by hammering in order to obtain homogenous compaction.

Column Equilibration

Greek sediment column was equilibrated with model water to obtain homogeneous condition of column soil. The boundary condition was set constant during the equilibration to the sorption phase. The process took place in the Thermostat with adjusted temperatur 10^oC.

When the equilibrium achieved, the column was ready to use in the sorption of cationic organic compound (Atenolol and Metoprolol). The inorganic cations of model water are shown in Table 2.

Table 2: Concentration of Inorganic Cations as Competitive Agents in Model Water

Water Types	Cation Concentration (Mg/L)			
	Na^+	K^+	Mg^{2+}	Ca^{2+}
Raw water	6.1	1.5	3.1	39.6
Model water (Equlibration phase)	6.1	1.5	3.1	39.6
Model water (Sorption phase)	200.1	39.9	92.5	81.8
Target water	202.2	41.1	93.0	81.9

Sorption Process

Atenolol 0,5 mg/L was added into the reservoir with well mixture after equilibrium of the column. Tracer experiment was included together with the sorption process using NaCl (1338.5 mg/L) for determination of tracer breakthrough curve. Steady flow 0.5 mL/min was applied onto the column in the experiments. Electrical conductivity was

monitored every 10 minutes until constant value achieved. By the similar method, column experiments using Metoprolol were conducted. The outlet of column experiment was collected every 10 minutes using fraction collector. The concentrations of these samples were analyzed using HPLC. When invariable concentration obtained, the sorption assumed has been equilibrated and the experiments can be terminated.

DOC Analysis

Dissolved organic carbon (DOC) was analyzed in the reservoir and outlet of equilibrium phase of the column. When the DOC of the product remains constant, it indicated that no organic matter was generated in the column. in this phase, the column has been equilibrated and ready to be continued with the next phase: sorption process. In addition, the DOC of sorption product was determined as well.

Sample of 30 mL was adjusted to acid condition after filtration through a 0.45 µm cellulose nitrate disposable filter. The measurement was accomplished using TOC-5000 Shimadzu. NPOC method was used, with the calibration range from 1 to 10 mg/L and detector limit 0.1 mg/L.

Compound Concentrations Analysis

Analysis of Atenolol and Metoprolol concentrations in the product were performed using High Performance Liquid Chromatography. The samples were filtrated with 0,45µm cellulose membrane filter and filled into the vials. The column phenomenex Gemini-NX 5µm C_{18} with dimension of 150 x 4.6 mm, under isocratic mobile phase using acetonitrile and ammonium hydrogen carbonate as eluents. Both analyses were operated with 0.3 mL/min flow rate of the mobile phase.

RESULTS AND DISCUSSIONS

DOC of Model Water and Column Outlet

The DOC determination is shown in Table 3. The analysis of DOC intended for the determination of the equilibrium of the column. When the equilibrium was achieved, which was no more organic generate in the column, the DOC in the inlet model water would be similar to the outlet. In this condition, it was ready to be used in the sorption of organic cationic compounds, Atenolol dan Metoprolol.

Equilibration of the column experiments required 6 – 7 days with constant flow of 0.5 mL/min continuously. The stage was incredibly important to eliminate another effect, such as another organic effect from the column (sediment) in the sorption of investigated compounds. Therefore, the sorption of investigated compounds (Atenolol and Metoprolol) would be dominant in the process.

Additional 0.5 mg/L Atenolol as well as Metoprolol has slightly enhanced the DOC concentration of the model water. However, after equilibrium, the DOC in the inlet and outlet of the system were significantly constant all the time (Table 3). Once the DOC increased as the compounds were introduced, it remained constant during the process.

The increase of DOC was due to the containing of 63% of C element in Atenolol structure. The injection 0.5 mg/L of the compound into the model water would heighten the DOC concentration up to 0.315 mg/L from the DOC of the basic model water. Theoretically, the value would be 0.315+2.68 = 2.995 mg/L.

It was comparable to the DOC from the analysis 0.3 mg/L. By the similar method, the Metoprolol contains of 67% C, thus the injection of the 0.5 mg/L Metoprolol concentration into model water have elevated the DOC up to 3.5 mg/L

Table 3: Average DOC of Model Water of Column Experiment

Phase	DOC [Mg/L]	
	Reservoir	Effluent
Equilibration		
at t = t_o	3.1	5.2
at t = t_{eq}	2.7	2.6
Sorption		
At t = t_o :		
Atenolol 0.5 mg/L	3.0	3.0
Metoprolol 0.5 mg/L	3.5	3.5
at t = t_{eq}:		
Atenolol 0.5 mg/L	3.0	3.0
Metoprolol 0.5 mg/L	3.5	3.5

t_o = initial time, t_{eq} = time after equilibrium of the column, the last day of equilibration phase or sorption phase. Eventually, it was obvious that the DOC concentration of the model water as well as the effluent were identical during the main phase experiments. It represented that the column was firmly equilibrated.

Conservative Tracer and Column Properties

Sodium chloride was used as conservative tracer in this research. The typical tracer curves from all experiments are shown in Figure 2. Excel Macros Program was employed in the measurement of ideal breakthrough time (t_r). On the other hand, manual calculation was performed as well.

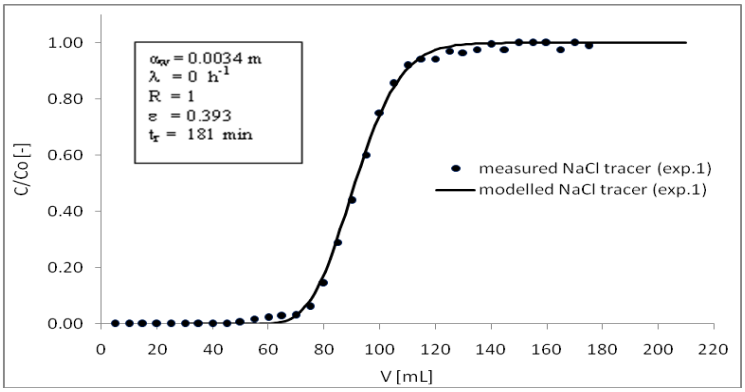

Figure 2: Conservative Tracer

The curves from experimental data were fitted to the model using Transmod Program from Worch in order to obtain the water transport parameters. Figure 2 represents a model curve of tracer tests in water retention on the Greek sediment. As a result, the average water retention time (t_r) in the column of Greek sediment in present research was 181 minutes. The bed porosity can be easily determined by using t_r by calculation using the Excel Macros Program. The average bed porosity was ~ 39 %. It was incredibly influenced by the certain type of sediment (Schaffer, 2010) and the compaction of the bed. If the sediment is not tightly compacted into the bed, less dense column will be produces. As consequence, higher porosity will be obtained. Less compact column would produce the diversity of retention time (Bi et al., 2010). Accordingly, it is principal to encompass comparable bed densities. However, the overall column porosities in this research were comparable enough to perform the experiments.

Tracer dispersivity showed a water dispersivity (α_w) in the column, where was 0.0034 m in this case. Retardation was unity which indicates no sorption of the tracer occurred on the sediment. No degradation (λ=0 h^{-1}) of the tracer took place in the column. Accordingly, sodium chloride was an appropriate conservative tracer to be used in this experiment.

Compounds Sorption Behavior

Concentration of Atenolol and Metoprolol were determined in the inlet water (reservoir) every day in order to get information about biological degradation of the compounds before entering the column. The result showed that the concentrations of both compounds remain constant in the reservoir during the experiments. Therefore, no degradation of Atenolol and Metoprolol occurred in the reservoir.

In addition, sampling of the outlet flow from the column was done every ten minutes by fraction collector during the sorption phase of the experiments. The concentrations of the samples were determined using HPLC until constant concentration obtained.

Metoprolol has a related structural formula with Atenolol except in one side where Atenolol contains O-NH_2 (polar) group while Metoprolol hold–CH_3 (nonpolar) group (Figure 1). They have similar pK_a (see Table 1), and pharmaceutically has similar function as adrenoreceptor in reducing hypertension. It was expected to have more or less similar chemical characteristics in the sorption. Due to the lack information provided in literature regarding the Metoprolol sorption characteristics, the present experiment was performed as the pre-information for further research.

The most important different between Atenolol and Metoprolol characteristics was the biodegradability. Atenolol was moderately degradable in the column of Greek sediment, even though in the adjusted temperature of 10^{o}C (see Figure 3). On the other hand, Metoprolol was more stable even in room temperature, consequently Metoprolol was easier to manage in this experiment.

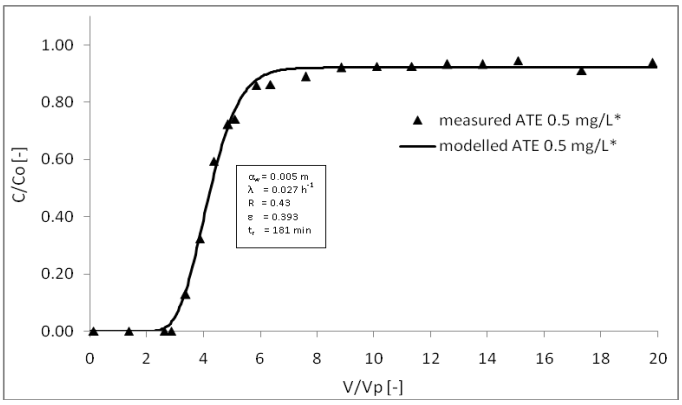

Figure 3: Sorption Characteristics of 0.5 Mg/L Atenolol on Greek Sediment and Modeled Curve

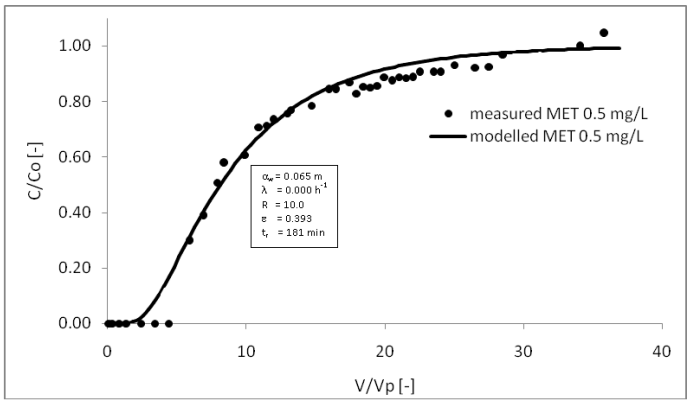

Figure 4: Sorption Characteristics of 0.5 Mg/L Metoprolol on Greek Sediment and Modeled Curve

Approximately three days was required for the sorption of 0.5 mg/L Atenolol to obtain breakthrough curve while Metoprolol needed roughly 4 days. The characteristics of Atenolol and Metoprolol sorption were shown in Figure 3 and 4. The dot curve indicates the experimental data, while the line curve is the modeled one. The sorption characteristics

obtained from the column experiments were fitted to the advection-dispersion equation (ADE). The model was run using the Transmod Program from Worch. The iteration of the sorption parameters (R, α_w, and λ) was done until the modeled curve were fitted to the experimental curves. For the conservative tracer parameter,

The iteration was required only for dispersion coefficient (α_w). It is because of no retardation (R = 1) and no degradation occurred (λ = 0). For simplification purposes, it is assumed that the filter velocity, bulk density, and dispersivity, are constant during the experiments. Additionally, the bed column was supposed to have a homogeneous porosity (Worch, 2011). Figure 3 and Figure 4 represent a great different of the retardation of Atenolol and Metoprolol. The transport parameters (R values) obtained were 4.3 for Atenolol and 10.0 for Metoprolol on the column of Greek sediment. Additionally, it was indicated the unsimetrical dot curve in the Metoprolol sorption.

Moreover, in spite of its persistence (Vieno et al., 2006) at certain boundary conditions, Atenolol was partially degraded (Figure 3). The decay rate (λ) was 0.027 h^{-1}. Although the experiments were carried out under controlled boundary temperature, the degradation was occurred during the sorption on the column.

It might be due to effect of biological activities in the column. The growth of microorganisms in the column could be consolidated with the slightly change temperature during preparation process. The degradation of ATE in the column experiments at a few magnitudes has affected the sorption process. However, the degradation rate and the possible causes were not taken into account in this research.

On the other hand, no degradation effect took place on the sorption of Metoprolol on the Greek sediment. Metoprolol is more stable even in room temperature rather than Atenolol.

Finally, Atenolol and Metoprolol showed a tremendously different sorption behavior onto Greek sediment. Atenolol was less retarded in the Greek sediment while Metoprolol has retardation factor almost two times of Atenolol in this experiment.

CONCLUSIONS

Atenolol and Metoprolol belong to the group of ß-blocker seemed to have almost similar properties. However, the sorption experiments of the compounds onto Greek sediment showed the Atenolol behavior differed from Metoprolol. Metoprolol depicted a strong tailing in the breakthrough curve. Retardation of the compound under the influence of **inorganic** competitive cations was virtually two times higher (R = 10.0) than Atenolol (R = 4.3) at equivalent boundary conditions. Metoprolol investigation seemed simpler to conduct due to the relative stable concentration in the room conditions.

REFERENCES

1. Bendz, D., Paxeus, N.A., Ginn, T.R, and Loge, F.J., 2005. Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden. J. of Hazardous Materials 122, 195-204.
2. Bi, E., Schmidt, T.C., Haderlein, S.B., 2010. Practical issues relating to soil column chromatography for sorption parameter determination. Chemosphere 80, 787-793.
3. BLAC-Bund/Länder-Arbeitsgemeinschaft Chemikaliensicherheit., 2003. Arztneinmittle in der Umwelt-Auswertung der Untersuchungsergebnisse. http://www.blac.de/servlet/is/2146/P-2c.pdf. Accessed: 21th September 2011.

4. Cleuvers, M., 2005. Initial risk assessment for three β-blockers found in the aquatic environment. Chemosphere 59, 199-205.

5. Farre, L.M., Perez, S., Kantiani, L., Barcelo, D., 2008. Fate and toxicity of emerging pollutants, their metabolites and transformation products in the aquatic environment. Trend in Analytical Chemistry, vol.27. No.11, 991.

6. Gros, M., Petrovic, M., and Barcelo, D., 2006. Development of a multi-residue analytical methodology based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters. Talanta 70, 678.

7. Heberer, T., 2002. Occurrence, fate and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol. Lett 131, 5-17.

8. Lundström, E., Adolfsson-Erici, M., Alsberg, T., Bjoerlenius, B., Eklund, B., Laven, M., Breitholtz, M., 2010. Characterization of additional sewage treatment technologies: Ecotoxicological effects and levels of selected pharmaceuticals, hormones and endocrine disruptors. Elsevier. Ecotoxicology and Environmental Safety 73, 1612.

9. Martinez, V., Maguregui M.I., Jimenez, R.M., Alonso, R.M., 2000. Determination of the pKa values of ß-blockers by automated potentiometric titrations. J. Pharmaceutical and Biomedical Analysis 23, 459-468.

10. Sires, I., Oturan, N., and Oturan, M.A., 2010. Electrochemical degradation of ß-blockers. Studies on single and multicomponent synthetic aqueous solutions. Water Research 44, 3109-3120.

11. Schaffer M., Börnick H., Nödler K., Licha T., Worch E., 2012. Role of cation exchange processes on the sorption influenced transport of cationic β-blockers in aquifer sediments. Water Research, 46,17, 5472-5482.

12. Song, W., Cooper, JW, Stephen, PM, Greaves, J., and Peake, MB., 2008. Free radical destruction of β-blockers in aqueous solution. Environ.Sci.Technol. 42, 1256-1261.

13. Ter Laak, T., van der Aa, M., Stoks, P., and van Wezel, A., 2010. Temporal and spatial trends of pharmaceuticals in the Rhine. Rhine Water Works (RIWA). The Netherland.

14. Varcarcel, Y., Gonzalez Alonso, S., Rodriguez-Gil, J.L., Romo Maroto, R., Gil, A, and Catala, M., 2011. Analysis of presence of cardiovascular and analgesic/anti-inflammatory/antipyretic pharmaceuticals in river-and drinking-water of the Madrid Region in Spain. Chemosphere 82, 1062-1071.

15. Vieno, M. N., Tuhkanen, T., Kronberg, L., 2006. Analysis of neutral and basic pharmaceuticals in sewage treatment plants and recipients rivers using solid phase extraction and liquid chromatography-tandem mass spectrometry detection. J. of Chromatography 1134, 101.

16. Worch, E., 2004. Modelling the solute transport under nonequilibrium condition on the basis of mass transfer equations. J. of Contaminant Hydrology 68, 97-120.

17. Yamamoto, H., Nakamura, Yu., Moriguchi, S., Nakamura Yi., Honda, Y., Tamura, I., Hirata, Y., Hayashi, A., and Sekiwaza, J., 2009. Persistence and partitioning of eight selected pharmaceuticals in the aquatic environment: Laboratory photolysis, biodegradation, and sorption experiments. ScienceDirect. JWater Research 43, 351-362.